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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/818,875	03/27/2001	Eric B. Kmiec	Napro-4	2466

1473 7590 11/05/2002

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EXAMINER
ANGELL, JON E

ART UNIT	PAPER NUMBER
1635	19

DATE MAILED: 11/05/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/818,875	Applicant(s) KMIEC ET AL.	
	Examiner J. Eric Angell	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8/23/02* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-38 and 40-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-38 and 40-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 15/16 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Action is in response to the amendment filed 8/23/02, as Paper No. 16. Claim 9 has been cancelled and claims 25, 26, 32, 50, 51, 52, 57, 58, 72 and 75 have been amended. The response to Applicant's arguments is included herein. Any rejections not reiterated are withdrawn.

Specification

1. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. For instance, page 11 lines 14-16 contain an embedded hyperlink. Applicant is required to delete all embedded hyperlinks and/or other form of browser-executable code. See MPEP § 608.01.

2. The disclosure is also objected to because of the following informalities: page 27 of the specification contains only three lines of text, leaving the rest of page 27 blank. Therefore, page 27 is not a complete page of text.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 25-28 and 29-77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably

convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 25 and 75 are drawn to a method of targeted sequence alteration of a nucleic acid comprising: combining the targeted nucleic acid in the presence of cellular repair proteins with a single stranded oligonucleotide 17-121 nucleotides in length, **said oligonucleotide having an internally unduplexed domain of at least 8 contiguous deoxyribonucleotides** (emphasis added).

However, the originally filed application does not disclose oligonucleotides having an internally unduplexed domain of at least 8 contiguous deoxyribonucleotides (emphasis added). In the amendment filed March 7, 2002, Applicants assert that support for an internally unduplexed domain of at least 8 contiguous nucleotides is found, for example, on page 7, line 20. It is noted that page 7, line 20 reads, "The central DNA domain is generally at least 8 nucleotides in length." There is no disclosure that can be found anywhere in the specification that the oligonucleotide comprises an internally unduplexed domain of at least 8 deoxyribonucleotides. Furthermore, it is not apparent in the figures that any of the oligonucleotides comprise an internally unduplexed domain of at least 8 contiguous deoxyribonucleotides. Therefore, the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claims 26-74, 76 and 77 are dependent claims and are rejected for the same reasons.

Response to Arguments

5. Applicant's arguments filed 8/23/02 have been fully considered but they are not persuasive.

Applicants argue that support for "internally unduplexed domain of at least 8 contiguous deoxyribonucleotides" can be found in the specification at 4 different places: 1) Specification page 7, lines 7-11; 2) Specification page 7, lines 17-22; 3) Specification page 7, lines 27-28; and 4) Figure 1. Applicants also refer to specification page 23, lines 7-10, which describes a previously disclosed double-stranded targeting oligonucleotide, but does not indicate a single stranded oligonucleotide or an internally unduplexed domain.

In response, it is respectfully pointed out that the indicated passages in the specification do not clearly indicate an internally unduplexed domain of at least 8 contiguous deoxyribonucleotides. 1) Specification page 7, lines 7-11 indicates that the oligonucleotide is single stranded, but it does not disclose an internally unduplexed domain of at least 8 contiguous deoxyribonucleotides. 2) Specification page 7, lines 17-22 indicates that the central DNA domain is generally at least 8 nucleotides in length, but it does not specifically disclose that the central DNA domain is unduplexed. 3) Specification page 7, lines 27-28 indicate that the oligonucleotides are "single stranded and are not designed to form a stable internal duplex structure within the oligonucleotide." However, this passage only indicates that the oligonucleotides are not designed to form a stable internal duplex structure, and does not clearly disclose that the oligonucleotide contains an internally unduplexed domain. It is respectfully pointed out that an oligonucleotide "not designed to form a stable internal duplex structure

within the oligonucleotide" would not necessarily contain an internally unduplexed domain of at least 8 contiguous deoxyribonucleotides.

Applicants also indicate that Figures 1A and 1B indicate single-stranded structures (III and V-XIII) which "are explicitly and correctly drawn to show the absence of such internal duplex". It is respectfully pointed out that Figures 1A and 1B disclose the generation of modified single-stranded oligonucleotides that contain (A) 2'-O-methyl RNA nucleotides or (B) phosphorothioate linkages (see description of figures, in amendment filed 3/7/02). Although Figures 1A and 1B appear to disclose the generation of single-stranded oligonucleotides, it is not clear that the oligonucleotides contain an internally unduplexed domain of at least 8 contiguous deoxyribonucleotides. Looking to the specification for guidance, the description of the Figure 1 makes no reference to any internally unduplexed domain. Therefore, it cannot be concluded that Figures 1A and 1B disclose a single stranded oligonucleotide comprising an internally unduplexed domain.

Although the specification has disclosed single stranded oligonucleotides comprising an internal DNA domain of at least 8 nucleotides in length (see the passages cited above), the originally filed application does not disclose oligonucleotides having an internally unduplexed domain of at least 8 contiguous deoxyribonucleotides (emphasis added).

6. Claims 25-38 and 40-77 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a targeted sequence alteration in a nucleic acid in a cell, wherein the cell is not present in a living organism and wherein the cell is not a human

stem cell, does not reasonably provide enablement for making a targeted sequence alteration in a nucleic acid in cell present in a living organism or in a human stem cell for stem cell therapy. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to a method for targeted sequence alteration of a nucleic acid using oligonucleotides, and encompass altering genetic material for the treatment of disease. The claims encompass making the genetic modification in a cell that is present in a living organism (i.e. in vivo) and encompasses making genetic alterations in human stem cells. Therefore the nature of the invention is a method of gene therapy, specifically, therapeutic gene targeting, and encompasses stem cell therapy.

The breadth of the claims

The breadth of the claims is very broad. For instance, the claims encompass gene targeting of any gene, in any cell type, in any species of animal, including humans. The claims

also encompass gene targeting in cells *in vitro, ex vivo* and *in vivo*. Furthermore, the claims encompass producing any type of genetic alteration, such as base substitution, and addition/deletion of any number of bases. The claims also encompass making genetic modifications to human stem cells which could be used for stem cell therapy.

The unpredictability of the art and the state of the prior art

At the time of filing, the relevant art considered gene therapy as a whole to be unpredictable as efficient modes of delivering therapeutic nucleic acid to target cells had not been developed. Currently, the state of the art of gene therapy is still in its infancy as the art is plagued by unpredictability. For instance, Crystal (Science, 1995; 270:404-409) teaches that all of the human gene therapy studies have been plagued by inconsistent results, and sites specific examples (see page 409, first col.). Verma et al (Nature, 1997; Vol. 389) teaches, "there is still no single outcome that we can point to as a success story" (see pg. 239, col. 1; Gene Therapy Promises, Problems and Prospects).

Regarding therapeutic gene targeting, Yanez et al. (Gene Therapy; Vol. 5, p. 149-159; 1998) teaches, "While gene targeting has been achieved both in human cell lines and in non-transformed primary human cells, its low efficiency has been a major limitation to its therapeutic potential. Gene therapy by in vivo gene targeting is therefore impractical without dramatic improvements in targeting efficiency. Ex vivo approaches might more realistically be considered, but would benefit from progress in the isolation and growth of somatic stem cells and improvements in targeting efficiency." (See abstract). Yanez also teaches that although reports that gene targeting using oligonucleotides have dramatically improved gene targeting frequencies, "Unfortunately, the logarithmic relationship between targeting efficiency and length

of homology suggests that simple nucleic acids with small regions of homology will not be sufficient." (See p.153, last paragraph). Regarding the reports that DNA-RNA hybrid oligonucleotides were able to correct a single base mutation of the β-globin gene in immortalized B cells from a patient with sickle cell anemia, Yanez remarks, "as has recently been pointed out, further controls are required to rule out the possibilities of screening artefacts and cell contamination. An unambiguous demonstration of targeted correction would involve the isolation of a clonal cell population bearing both a corrected β-globin allele (as judged by Southern analysis) and an otherwise patient-specific genotype (as judged e.g. by DNA-fingerprint analysis)." (See p. 154, first paragraph). Yanez states in the final remarks that, "Many old and new questions remain unanswered. We do not understand why different loci appear to target at different frequencies, and whether this may be related to epigenetic factors such as DNA methylation or chromatin condensation. It is unknown how the proteins of HR [homologous recombination] are recruited to the DSB [double strand break], and little is known about the decision making that drives DSB repair to NHR [non-homologous recombination] and HR" and, " In vivo gene therapy by gene targeting is not viable at present." (See p. 156, under Final Remarks).

More recently, regarding the use of oligonucleotides for targeted gene repair, Gamper et al. (Nucleic Acids Research; Vol. 28, No. 21:4332-4339; 2000) states that the frequency of repair "still represents only a 0.1%-0.2% conversion rate, we may be moving closer to direct applications of gene repair in vivo." (See p. 4338, last paragraph). Indicating that the efficiency of targeted repair still needs improvement. Furthermore, Culver et al. (Nature Biotech. Vol. 17:989-993; 1999) indicates that, "Further experiments with bifunctional oligonucleotides are

needed to optimize their structural design, fully characterize the limits on size of mutations that can be repaired, and determine the influences of the various components of the DNA repair complex on the efficiency of correction." (See p. 992, third paragraph).

The claims are also drawn to targeting of nucleic acids in human embryonic stem cells, a method that encompasses stem cell therapy. Regarding stem cell therapy, Kaji et al. (JAMA, Vol. 285, No. 5:545-550; 2001) teaches, "Much additional work remains to be done in the areas of vector development and stem cell biology before the full therapeutic potential of these approaches can be realized. Of equal importance, the ethical issues surrounding gene- and cell-based therapies must be confronted." (See abstract, p. 545).

Working Examples and Guidance in the Specification

The specification has no working example of using oligonucleotides for successful targeted alteration in a cell that is in a living organism. Nor does the specification disclose working examples wherein cells that have been genetically altered were successfully used to treat any disease or disorder. The only examples disclosed are of successful alteration of an episomal nucleic acid in yeast (Example 2, p. 32), and successful genetic alteration in cell-free extracts (pages 26, 28, 29 and 31). However, as mentioned above, the claims encompass altering genetic material in a cell in a living organism (i.e. in vivo), and includes genetically altering human stem cells which could be used in stem cell therapy. There are no examples of successful targeting of any type of nucleic acid (such as RNA or chromosomal DNA) in a living cell other than a yeast cell. There are no working examples of successful gene targeting in cells present in a living organism. There are a number of possible genetic disorders that are mentioned as candidates for gene targeting (see Examples 3-25), and the possibility of genetically altering

plants using oligonucleotides is also mentioned (see Example 26); however, these examples (Examples 3-26) are only prophetic, and do not disclose the successful alteration of genetic material.

Quantity of Experimentation

The quantity of experimentation in this area is extremely large since determination of the efficacy of targeted alteration of genetic material in the large genus of species and of the types of alterations encompassed by the claims would require experimentation testing base addition, deletion and alteration in prokaryotic as well as plant and animal cells, including human cells. Furthermore, experimentation is required to determine the efficacy of gene alteration in vivo in plants and animals. Successful in vivo application in animals is required before in vivo clinical trials in humans can be performed. That is, prior to any therapeutic intervention, it would be necessary to successfully alter genetic material in animal models, in such a way that the genetic alteration treated a disease/disorder, an inventive, unpredictable and difficult undertaking in itself. After experimentation in the animal model(s), the efficacy of the treatment would have to be tested in human subjects. This would require years of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability of gene therapy (including therapeutic gene targeting) recognized in the art, the breadth of the claims, the lack of working examples and

guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to perform the broadly claimed method is undue.

Response to Arguments

7. Applicant's arguments filed 8/23/02 have been fully considered but they are not persuasive.

It is acknowledged that claims 25 and 75 have been amended to state "cellular repair proteins present within selectively enriched cells, cells in culture, or cell-free extracts". It is respectfully pointed out that the new limitation does not limit the method to alteration of nucleic acids wherein the alteration takes place within a selectively enriched cell, a cell in culture, or in a cell free-extract, only that the method comprises combining the targeted nucleic acid in the presence of cellular repair proteins present within selectively enriched cells, cells in culture, or cell-free extracts. Therefore the claims still encompass making genetic alteration in cells that are in a living organism (i.e. in vivo). Amending the claim to state that the targeted nucleic acid is in an isolated cell in culture or in a cell-free extract would limit the method to in vitro embodiments. However, the claims would still encompass therapy including human stem cell therapy, embodiments which are not enabled.

Regarding the applicants argument that the specification discloses examples indicating the alteration of targeted genetic material in yeast and in cell-free extracts, it is acknowledged that such examples are present in the specification. However, the specification does not have examples regarding the alteration of targeted nucleic acids in a cell in vivo (in a living organism) or that the method can be used as a form of therapy, such as in human stem cell therapy. It is respectfully pointed out that the claims still encompass the alteration of genetic material in a cell

in vivo and therapeutic treatment of disease using the altered cells (including human stem cell therapy), and these embodiments of the claims are not enabled.

Claim Rejections - 35 USC § 112

Response to Arguments

8. The rejection of claims under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in light of the amendments to the claims.

Claim Rejections - 35 USC § 102

Response to Arguments

9. The rejection of claims under 35 U.S.C. 102(b) as being anticipated by Sayers et al. (Nucleic Acids Research Vol. 16, No. 3:791-802; 1988) is withdrawn.

Conclusion

No claim is allowed.

10. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
October 27, 2002

JEFFREY FREDMAN
PRIMARY EXAMINER